

REMARKS

Claims 1-56 were pending in this application. Claims 38-48, 54 and 56 are withdrawn as drawn to non-elected Groups. In addition, claims 11, 31, 33 and 49 have been amended to remove subject matter drawn to non-elected groups. Applicants expressly reserve the right to pursue protection of any or all of the subject matter of these cancelled or amended claims in a subsequent application. Applicants further reserve the right to pursue the subject matter of claims drawn to any groups the Examiner declines to recombine in response to this filing.

Moreover, six paragraph(s) of the specification have been amended to correct obvious clerical errors in nucleic acid and amino acid sequence identifiers, and the Sequence Listing has been replaced.

No new matter is introduced by the amendments made herein. Unless specifically stated otherwise, none of these amendments are intended to limit the scope of any claim. After entry of these amendments **claims 1-37, 49-53 and 55 are pending in this application.** Consideration of the pending claims is requested.

Correction of Clerical Errors

The specification has been amended to correct obvious clerical errors in the assignment of nucleic acid and sequence identifiers (at pages 28, 69, and 70). The specification clearly demonstrates at page 8, line 7-8 and page 8, lines 13-14 that SEQ ID NOS: 18, 19, 22 and 23 are oligonucleotide primer sequences not nucleic acid sequences encoding, or amino acid sequences of, TGF- β 1 fusion proteins, as they were erroneously referred to in the specification. To correct this, sequence identifiers SEQ ID NO: 16 and SEQ ID NO: 17 have been substituted for SEQ ID NOS: 18 and 19 when referring to N+5FLAG-TGF- β 1, and SEQ ID NO: 20 and SEQ ID NO: 21 have been substituted for SEQ ID NOS: 22 and 23 when referring to N+5HA-TGF- β 1. Support for these corrections may be found, e.g., at page 8, lines 3-6 in the original specification, and in SEQ ID NOS: 16, 17, 20 and 21 in the original Sequence Listing.

Certain descriptors relating to SEQ ID NOs: 36 and 38 have been corrected from “N+5FLAG-TGF- β 1” to “N+5-HA TGF- β 1” to show the correct tag (at pages 28 and 69). These correction are supported at least by SEQ ID NOs: 36 and 38 in the original Sequence Listing, which clearly show the nucleic acid and deduced protein sequences for an “HA” tag (described, e.g., in original Figure 6) at the N+5 position.

The description of SEQ ID NO: 36 has been corrected to recite the “active” form of TGF- β 1 fusion protein (at page 9). This correction is supported, e.g., by the descriptor “actN5HAb1” (emphasis added) at page 9, line 10 in the original specification, and by SEQ ID NO: 36 in the original Sequence Listing.

The description of SEQ ID NO: 38 has been corrected to recite the “latent” form of TGF- β 1 fusion protein (at page 9). This correction is supported, e.g., by the descriptor “latN5HAb1” (emphasis added) at page 9, line 14 in the original specification, and by SEQ ID NO: 38 in the original Sequence Listing.

Finally, the obvious typographical error of “SEQ ID NO: 376” has been corrected to “SEQ ID NO: 37” at pages 28 and 70.

Replacement Sequence Listing

Applicants submit herewith a replacement electronic copy (diskette) of the Sequence Listing, and a corresponding paper copy (64 pages). In compliance with 37 C.F.R. § 1.821(f), the undersigned declares that the nucleotide sequences presented in the paper copy of the Sequence Listing submitted herewith are the same as the sequences contained in the computer-readable form of the Sequence Listing.

In the replaced sequence listing, SEQ ID NO: 10 (representing the mature form of NFLAG-TGF- β 1) was corrected by insertion of an adenine nucleotide between positions 139 and 140 so that SEQ ID NO: 10 accurately corresponds to the mature portion of NFLAG-TGF- β 1 represented by residues 835-1197 of SEQ ID NO: 8. This correction is supported, e.g., at page 7, lines 10-11, at page 7 lines 16-17 and by SEQ ID NO: 8 in the specification as originally filed.

Similarly, SEQ ID NO: 14 (representing the mature form of 11/12FLAG-TGF- β 1) was corrected by insertion of a guanine nucleotide between positions 199 and 200 so that SEQ ID NO: 14 accurately corresponds to the mature portion of 11/12FLAG-TGF- β 1 represented by residues 835-1197 of SEQ ID NO: 12. This correction is supported, e.g., at page 7, lines 20-23, at page 7 lines 28-29 and by SEQ ID NO: 12 in the original specification. It is believed that no new matter is introduced by these amendments, and that they would have been apparent to a person of ordinary skill in the art.

First Restriction Requirement

Applicants elect Group I (claims 1-37 and 49-56), drawn to a functional TGF- β family fusion protein, isolated nucleic acid molecule, vectors, and cells comprising the same.

Second Restriction Requirement

Applicants traverse the restriction of claims 1-56 under 35 U.S.C. §121 into Groups A-Z, AA and BB. The Examiner contends that the claims are directed to several patentably distinct inventions because allegedly each sequence requires a separate search of the literature and sequence databases, which allegedly presents the Examiner with an undue search burden.

It is respectfully submitted that the claims encompassing sequences set forth in SEQ ID NOs: 8-15 and 32-39 (i.e., Groups A-H, U-Z, AA and BB) could readily be examined together in the same application, because all of the claims relate to **functionalized porcine TGF- β 1** fusion proteins, isolated nucleic acids, vectors, and cells comprising the same. Specifically, Groups A-H and U-X relate to FLAG-tagged porcine TGF- β 1 amino acid and nucleic acid sequences (SEQ ID NOs: 8-15 and 32-35), and Groups Y, Z, AA and BB (SEQ ID NOs: 36-39) relate to HA-tagged porcine TGF- β 1 amino acid and nucleic acid sequences. Groups A, C, E, G, U, W, Y, and AA relate to tagged porcine TGF- β 1 *nucleic acid sequences*, and Groups B, D, F, H, V, X, Z, and BB relate to the corresponding *amino acid sequences*.

To assist the Examiner in recognizing how similar these sequences truly are, an alignment of the relevant portions of the Groups A (SEQ ID NO: 8), C (SEQ ID NO: 10), E

(SEQ ID NO: 12), G (SEQ ID NO: 14), U (SEQ ID NO: 32), W (SEQ ID NO: 34), Y (SEQ ID NO: 36), and AA (SEQ ID NO: 38) nucleic acid sequences is shown below:

SEQIDNO8	CCC ACT CTT CCT CTG ACAG CAA AGATA AAC AC ACT CCAC GTGG AATT AAC CGGG TTCA ATT	721
SEQIDNO10	-----	
SEQIDNO12	CCC ACT CTT CCT CTG ACAG CAA AGATA AAC AC ACT CCAC GTGG AATT AAC CGGG TTCA ATT	721
SEQIDNO14	-----	
SEQIDNO32	CCC ACT CTT CCT CTG ACAG CAA AGATA AAC AC ACT CCAC GTGG AATT AAC CGGG TTCA ATT	731
SEQIDNO34	CCC ACT GTT CCT GTG ACAG CAA AGATA AAC AC ACT CCAC GTGG AATT AAC CGGG TTCA ATT	735
SEQIDNO36	CCC ACT CTT CCT CTG ACAG CAA AGATA AAC AC ACT CCAC GTGG AATT AAC CGGG TTCA ATT	731
SEQIDNO38	CCC ACT GTT CCT GTG ACAG CAA AGATA AAC AC ACT CCAC GTGG AATT AAC CGGG TTCA ATT	731
SEQIDNO8	CTGGCCGCCGGGGTGACCTGCCACCATTACGGCATGAACCGGCCCTCCTGCTCCTCA	781
SEQIDNO10	-----	
SEQIDNO12	CTGGCCGCCGGGGTGACCTGCCACCATTACGGCATGAACCGGCCCTCCTGCTCCTCA	781
SEQIDNO14	-----	
SEQIDNO32	CTGGCCGCCGGGGTGACCTGCCACCATTACGGCATGAACCGGCCCTCCTGCTCCTCA	791
SEQIDNO34	CTGGCCGCCGGGGTGACCTGCCACCATTACGGCATGAACCGGCCCTCCTGCTCCTCA	795
SEQIDNO36	CTGGCCGCCGGGGTGACCTGCCACCATTACGGCATGAACCGGCCCTCCTGCTCCTCA	791
SEQIDNO38	CTGGCCGCCGGGGTGACCTGCCACCATTACGGCATGAACCGGCCCTCCTGCTCCTCA	791
SEQIDNO8	TGGCCACCCGCTGGAGAGGGCCCAGCACCTGCACAGCTCCGGCACCGCCGAG-----	835
SEQIDNO10	-----G-----	1
SEQIDNO12	TGGCCACCCGCTGGAGAGGGCCCAGCACCTGCACAGCTCCGGCACCGCCGAGCCCTGG	841
SEQIDNO14	-----GCCCTGG-----	7
SEQIDNO32	TGGCCACCCGCTGGAGAGGGCCCAGCACCTGCACAGCTCCGGCACCGCCGAGCCCTGG	851
SEQIDNO34	TGGCCACCCGCTGGAGAGGGCCCAGCACCTGCACAGCTCCGGCACCGCCGAGCCCTGG	855
SEQIDNO36	TGGCCACCCGCTGGAGAGGGCCCAGCACCTGCACAGCTCCGGCACCGCCGAGCCCTGG	851
SEQIDNO38	TGGCCACCCGCTGGAGAGGGCCCAGCACCTGCACAGCTCCGGCACCGCCGAGCCCTGG	851
SEQIDNO8	-----ACTAC--A-AGGATG-AC--GACGACA-A-----GGC-CC-TGGA-TACCA	871
SEQIDNO10	-----ACTAC--A-AGGATG-AC--GACGACA-A-----GGC-CC-TGGA-TACCA	37
SEQIDNO12	ATACCA---ACTAC-----TG-C-----TT-CA-----GCTCCACGGACTAC-A	874
SEQIDNO14	ATACCA---ACTAC-----TG-C-----TT-CA-----GCTCCACGGACTAC-A	40
SEQIDNO32	ATACCAACGACTAC--A-AGGATG-AC--GACGACA-A-----GGC-CC-TGGA-TACCA	896
SEQIDNO34	ATACCAACGACTAC--A-AGGATG-AC--GACGACA-A-----GGC-CC-TGGA-TACCA	900
SEQIDNO36	ATACCAACAGCTACCCATACGACGTGCCAGACTACGCATCTGGC-CC-TGGA-TACCA	908
SEQIDNO38	ATACCAACAGCTACCCATACGACGTGCCAGACTACGCATCTGGC-CC-TGGA-TACCA	908
SEQIDNO8	ACTACTGCTTCAGCTCCACGGAGAAGAACTGCTGCGTGCAGCTCT	919
SEQIDNO10	ACTACTGCTTCAGCTCCACGGAGAAGAAACTGCTGCGTGCAGCTCT	85
SEQIDNO12	AGGA-TG--ACGACGACAAGGAGAAGAAACTGCTGCGTGCAGCTCT	919
SEQIDNO14	AGGA-TG--ACGACGACAAGGAGAAGAAACTGCTGCGTGCAGCTCT	85
SEQIDNO32	ACTACTGCTTCAGCTCCACGGAGAAGAAACTGCTGCGTGCAGCTCT	944
SEQIDNO34	ACTACTGCTTCAGCTCCACGGAGAAGAAACTGCTGCGTGCAGCTCT	948
SEQIDNO36	ACTACTGCTTCAGCTCCACGGAGAAGAAACTGCTGCGTGCAGCTCT	956
SEQIDNO38	ACTACTGCTTCAGCTCCACGGAGAAGAAACTGCTGCGTGCAGCTCT	956

Except for the positions indicated in gray shading above, the entire lengths of the eight functionalized porcine TGF- β 1 sequences are identical (including the portions not reproduced in

this response). Overall, there is at least 93% sequence identity among the nucleic acid sequences in Groups A, C, E, G, U, W, Y, and AA (which is well within the 85% limitation currently in claim 1). Accordingly, it is respectfully submitted that a search for any one of the sequences in Groups A, C, E, G, U, W, Y, and AA will necessarily identify references that implicate the subject matter of all of Groups A, C, E, G, U, W, Y, and AA. Thus, minimal additional PTO resources will be required to search and examine all of claims 1-37 and 49-56 as they pertain to Groups A, C, E, G, U, W, Y, and AA.

In addition, MPEP 803.04 states that “up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.” Groups A, C, E, G, U, W, Y, and AA represent eight nucleic acid sequences, which clearly falls within the number allowed by the MPEP. Thus, a search of less than ten, highly homologous sequences (at least 93% identity) would not impose an undue search burden.

By restricting the claims to proteins and nucleic acids in Group I in the first restriction requirement (which has been elected by the Applicants), the Examiner has already determined that proteins and nucleic acids should be examined together. Hence, if the functionalized porcine TGF- β 1 nucleic acid sequences (*i.e.*, Groups A, C, E, G, U, W, Y, and AA) are examined together, then the amino acid sequences encoded by those nucleic acid sequences (*i.e.*, Groups B, D, F, H, V, X, Z, and BB) should be examined with the nucleic acid sequences.

Therefore, Applicants request that all of the sequences in Groups A-H and U-X be examined together.

Alternatively, Applicants request that Group Z (SEQ ID NO: 37) be examined with provisionally elected Group Y (SEQ ID NO: 36), because the nucleic acid sequence in Group Y encodes the amino acid sequence in Group Z. The Examiner has determined that protein and nucleic acid sequences should be examined together. Hence, it would be inconsistent with the restriction requirement itself to require an election between Groups Y and Z.

Third Restriction Requirement

Applicants traverse the restriction of claims 1-56 under 35 U.S.C. §121 into Groups i-iv. The Examiner contends that each category of functionalizing peptide portion requires a separate search of the literature databases, which allegedly presents the Examiner with an undue search burden.

A single search for the TGF- β family nucleic acid or protein sequence into which the functionalizing peptide portion is inserted (e.g., a search of generic claim 25) will necessarily reveal any or all functionalized variants of the TGF- β molecule. Thus, it is not necessary to search the individual functionalizing peptide portions. Applicants respectfully submit that a single search of a TGF- β family nucleic acid or protein sequence does not present an undue search burden on the Examiner, and request that Groups i-iv be examined together.

CONCLUSIONS

It is respectfully submitted that the application is in condition for substantive examination. If any minor matters remain prior to examination, the Examiner is invited to call the undersigned at the telephone number listed below.

Respectfully submitted,

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**Marked-up Version of Amended Specification and Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)**

In the Specification:

At page 9, lines 9-10:

SEQ ID NO: 36 shows the nucleic acid and deduced protein sequence of the precursor

| porcine ~~latent~~-active N+5FLAG-5HA TGF- β 1 (actN5HAb1) fusion.

At page 9, lines 13-14:

SEQ ID NO: 38 shows the nucleic acid and deduced protein sequence of the precursor

| porcine active-latent N+5FLAG-5HA TGF- β 1 (latN5HAb1) fusion.

At page 28, line 24 through page 29, line 12:

In other examples of fusion proteins in which the functionalizing peptide is inserted within the mature TGF- β family protein, a portion of the TGF- β family protein may be repeated both before and after the inserted peptide. For instance, in some specific examples, the peptide is inserted after five amino acid residues of the mature TGF- β family protein, and these five amino acids are then repeated after the peptide (such that the entire TGF- β mature protein occurs in the fusion after the peptide). Such a fusion protein is exemplified by N+5FLAG-TGF- β 1 (SEQ ID NOS: 18 & 1916 & 17); N+5HA-TGF- β 1 (SEQ ID NOS: 22 & 2320 & 21); N+5FLAG TGF- β 2 (SEQ ID NOS: 24 & 25); N+5HA TGF- β 2 (SEQ ID NOS: 26 & 27); N+5FLAG TGF- β 3 (SEQ ID NOS: 28 & 29); N+5HA TGF- β 3 (SEQ ID NOS: 30 & 31); N+5FLAG TGF- β 1 (SEQ ID NOS: 32 & 33); N+5FLAG-TGF- β 1 (SEQ ID NOS: 34 & 35); N+5FLAG-5HA TGF- β 1 (SEQ ID NOS: 36 & 37637); and N+5FLAG-5HA TGF- β 1 (SEQ ID NOS: 38 & 39). Though these illustrated fusions have the peptide inserted after five amino acids of the mature TGF- β family protein, it could be inserted after a different number of amino acids, for instance, after one, after two, after three, after four, after six, after seven, or after eight amino acids. In this particular class of constructs, the amino acid residues of the mature TGF- β family protein that are located before (amino-terminal to) the functionalizing peptide are usually also repeated after the peptide, though they need not all be repeated.

At page 69, lines 5-18:

Additional functionalized TGF- β fusion proteins have been constructed in a manner essentially similar to the methods described in Examples 3 and 4. Specific examples of additional functionalized fusions include:

murine N+5FLAG TGF- β 2 (MN5FLAGb2; SEQ ID NO: 24 and 25);

murine N+5HA TGF- β 2 (MN5HAb2; SEQ ID NO: 26 and 27);

murine N+5FLAG TGF- β 3 (MN5FLAGb3; SEQ ID NO: 28 and 29);

murine N+5HA TGF- β 3 (MN5HAb3; SEQ ID NO: 30 and 31);

porcine active N+5FLAG TGF- β 1 (actN5FLAGb1; SEQ ID NO: 32 and 33);

porcine latent N+5FLAG TGF- β 1 (latN5FLAGb1; SEQ ID NO: 34 and 35) (made latent by mutations at positions 682 and 688 of SEQ ID NO: 34);

porcine active N+5FLAG-5HA TGF- β 1 (actN5HAb1; SEQ ID NO: 36 and 37); and

porcine latent N+5FLAG-5HA TGF- β 1 (latN5HAb1; SEQ ID NO: 38 and 39) (made latent by mutations at positions 678 and 684 of SEQ ID NO: 38).

At page 69, lines 19-21:

Additional characteristics of each of these fusions, as well as N+5FLAG-TGF- β 1 (SEQ ID NOS: 18-16 and 1917) and N+5HA-TGF- β 1 (SEQ ID NO: 22-2320 and 21) fusions, are provided in Table 2.

At page 70, lines 1-3:

Table 2

Fusion name and SEQ ID NOs.	5'UTR	CDS	3'UTR	AA 1-5 of TGF-β	Epitope tag	Mature fusion
N+5FLAG-TGF-β1 (NOS: 18 & 19 <u>16</u> & 17) ¹	1-347 ²	348-1559	1560-1612	1182-1196	1197-1220	182-1559
N+5HA-TGF-β1 (NOS: 22 & 23 <u>20</u> & 21)	1-347	347-1571	1572-1624	1182-1196	1197-1232	1182-1571
N+5FLAG TGF-β2 (NOS: 24 & 25)	N/A	1-1284	N/A	907-921	922-945	907-1284
N+5HA TGF-β2 (NOS: 26 & 27)	1-7	8-1303	N/A	914-928	929-964	914-1303
N+5FLAG TGF-β3 (NOS: 28 & 29)	N/A	1-1272	N/A	895-909	910-945	895-1272
N+5HA TGF-β3 (NOS: 30 & 31)	N/A	1-1284	N/A	895-909	910-945	895-1284
N+5FLAG TGF-β1 (NOS: 32 & 33)	1-10	11-1222	1223-1349	845-859	860-883	845-1222
N+5FLAG-TGF-β1 (NOS: 34 & 35)	1-14	15-1226	1227-1253	849-863	864-887	849-1226
N+5FLAG TGF-β1 (NOS: 36 & 37 <u>37</u>)	1-10	11-1234	1235-1361	845-859	860-895	845-1234
N+5FLAG TGF-β1 (NOS: 38 & 39)	1-10	11-1234	1335-1361	845-859	860-895	845-1234

¹Refers to the nucleic acid sequence and amino acid sequence for the listed fusion.²Residue positions correspond to the position in the nucleic acid sequence.**In the Claims:**

11. (amended) The fusion protein of claim 10, where the protein comprises the amino acid sequence as in SEQ ID NO: 11, SEQ ID NO: 15, ~~the mature portion of SEQ ID NO: 17, the mature portion of SEQ ID NO: 21, the mature portion of SEQ ID NO: 33, the mature portion of SEQ ID NO: 35, the mature portion of SEQ ID NO: 3539, the mature portion of SEQ ID NO: 37, or conservative substitutions thereof.~~

31. (amended) The isolated nucleic acid molecule of claim 30, comprising a sequence selected from the group consisting of:

- (a) nucleic acid residues 835 to 1197 of SEQ ID NO: 8;
- (b) SEQ ID NO: 10;
- (c) residues 835 to 1197 of SEQ ID NO: 12;
- (d) SEQ ID NO: 14;

- (e) ~~residues 182-1559 of SEQ ID NO: 18;~~
- (f) ~~residues 1182-1571 of SEQ ID NO: 22;~~
- (g) ~~residues 907-1284 of SEQ ID NO: 24;~~
- (h) ~~residues 914-1303 of SEQ ID NO: 26;~~
- (i) ~~residues 895-1272 of SEQ ID NO: 28;~~
- (j) ~~residues 895-1284 of SEQ ID NO: 30;~~
- (k) residues 845-1222 of SEQ ID NO: 32;
- (l) residues 849-1226 of SEQ ID NO: 34;
- (m) residues 845-1234 of SEQ ID NO: 36;
- (n) residues 845-1234 of SEQ ID NO: 38;

and

- (o) conservative variants of any one of (a) through (n).

33. (amended) The isolated nucleic acid molecule of claim 30, comprising a sequence selected from the group consisting of:

- (a) SEQ ID NO: 8;
- (b) SEQ ID NO: 12;
- (c) ~~SEQ ID NO: 18;~~
- (d) ~~SEQ ID NO: 22;~~
- (e) ~~SEQ ID NO: 24;~~
- (f) ~~SEQ ID NO: 26;~~
- (g) ~~SEQ ID NO: 28;~~
- (h) ~~SEQ ID NO: 30;~~
- (i) SEQ ID NO: 32;
- (j) ~~SEQ ID NO: 34;~~
- (k) ~~SEQ ID NO: 36; and~~
- (l) ~~SEQ ID NO: 38~~

49. (amended) A purified functional TGF- β fusion protein, comprising an amino acid sequence selected from the group consisting of:

- (a) SEQ ID NO: 9;

- (b) SEQ ID NO: 11;
- (c) SEQ ID NO: 13;
- (d) SEQ ID NO: 15;
- (e) ~~SEQ ID NO: 21;~~
- ~~(f) SEQ ID NO: 25;~~
- ~~(g) SEQ ID NO: 27;~~
- ~~(h) SEQ ID NO: 29;~~
- ~~(i) SEQ ID NO: 31;~~
- ~~(j) SEQ ID NO: 33;~~
- ~~(kf) SEQ ID NO: 35;~~
- ~~(tg) SEQ ID NO: 37;~~
- ~~(mh) SEQ ID NO: 39;~~
- ~~(ni) sequences having 85% sequence identity to any one of (a) through (mh);~~

and

- ~~(ej) conservative substitutions thereof.~~